Summer 8-11-2012

Deflazacort Versus Prednisone: A Systematic Comparison of two Steroids in the Treatment of Duchenne Muscular Dystrophy

Jaime L. Ulrich
Pacific University

Deflazacort Versus Prednisone: A Systematic Comparison of two Steroids in the Treatment of Duchenne Muscular Dystrophy

Abstract

Background: Duchenne muscular dystrophy (DMD) is a genetic disorder in males resulting in muscle weakness leading to loss of ambulation and progression to death by pulmonary and cardiac dysfunction. It has been documented both steroids deflazacort and prednisone delay muscle degeneration but not many studies outline the differences between the two including side effect profiles. Deflazacort is not yet available in the US. This systematic review compiles recent data to compare deflazacort to prednisone in the treatment of DMD boys.

Method: A full search of medical literature using multiple databases, MEDLINE, CINAHL, Evidence Based Reviews Multifile and Web of Science, and reference lists was conducted with the key words muscular dystrophy, deflazacort and prednisone. Articles that consisted of the outcomes of muscle function, cardiac and pulmonary changes, side effect incidence and type, and gene expression in whole blood were included. The literature was assessed using the GRADE system to rate its quality and importance.

Results: Four articles were selected for review. There were no significant differences between the two steroids in treating muscle functionality, prevention of cardiomyopathy or difference in pulmonary function. In Bonifati et al and Balaban et al, weight gain in prednisone-treated patients was greater than with deflazacort. With regards to gene expression, Lit et al discovered gene probes in the prednisone-treated patients which promote weight gain. On the other hand, deflazacort probes are suspected to prevent obesity.

Conclusion: It is clear both steroids are efficacious in treating DMD but side effects will determine patient and providers' choice of prescription. Further research with randomized control trails over extended time periods is needed to establish the true difference between side effects of deflazacort and prednisone. Research in gene expression holds promise for future utility in the selection of steroid therapy.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
Robert P. Rosenow, Pharm.D., O.D.

Second Advisor
Annjanette Sommers PA-C, MS

Keywords
Duchenne muscular dystrophy, steroids, deflazacort, prednisone

NOTICE TO READERS

This work is not a peer-reviewed publication. The Master's Candidate author of this work has made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.

Deflazacort Versus Prednisone: A Systematic Comparison of two Steroids in the Treatment of Duchenne Muscular Dystrophy

Jaime Lynn Ulrich

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11, 2012

Faculty Advisor: Dr. Rosenow

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Jaime Lynn hales from Steeler Country where she grew up with her older brother John and loving parents. In high school, Jaime knew she wanted to be involved in the medical field and participated in the Student Athletic Training program to learn more about medicine in the athletic population. She decided to explore Athletic Training as a career and at the University of Pittsburgh graduated with a Bachelors of Science in Athletic Training. Jaime realized Athletic Training was not her passion and instead searched for other opportunities. Working as a patient care technician at the Children's Hospital of Pittsburgh UPMC in the ER, she discovered her desire to become a Physician Assistant. She is now enrolled at Pacific University in the Physician Assistant program and has been traveling the United States for her clinical rotations. With her background in athletics and pediatrics, Jaime would like pursue a career in pediatrics.

Abstract

Background: Duchenne muscular dystrophy (DMD) is a genetic disorder in males resulting in muscle weakness leading to loss of ambulation and progression to death by pulmonary and cardiac dysfunction. It has been documented both steroids deflazacort and prednisone delay muscle degeneration but not many studies outline the differences between the two including side effect profiles. Deflazacort is not yet available in the US. This systematic review compiles recent data to compare deflazacort to prednisone in the treatment of DMD boys.

Method: A full search of medical literature using multiple databases, MEDLINE, CINAHL, Evidence Based Reviews Multifile and Web of Science, and reference lists was conducted with the key words muscular dystrophy, deflazacort and prednisone. Articles that consisted of the outcomes of muscle function, cardiac and pulmonary changes, side effect incidence and type, and gene expression in whole blood were included. The literature was assessed using the GRADE system to rate its quality and importance.

Results: Four articles were selected for review.[1-4] There were no significant differences between the two steroids in treating muscle functionality, prevention of cardiomyopathy or difference in pulmonary function. In Bonifati et al[1] and Balaban et al,[2] weight gain in prednisone-treated patients was greater than with deflazacort. With regards to gene expression, Lit et al[4] discovered gene probes in the prednisone-treated patients which promote weight gain. On the other hand, deflazacort probes are suspected to prevent obesity.

Conclusion: It is clear both steroids are efficacious in treating DMD but side effects will determine patient and providers' choice of prescription. Further research with randomized control trails over extended time periods is needed to establish the true difference between side effects of deflazacort and prednisone. Research in gene expression holds promise for future utility in the selection of steroid therapy.

Keywords: Duchenne muscular dystrophy, steroids, deflazacort, prednisone

Acknowledgements

To *Mom and Dad*: Thank you for all your support all my life, for bringing me into this world and showing me I can do anything I set my heart to. I'm lucky to have you at my back while I look towards my future.

To *Johnny*: Thank you for being my secret protector and rock. I'm proud to be your little sis.

To *Dr. Pellet*: Thank you for giving me the desire to know more about Duchenne muscular dystrophy. You are an amazing medical provider and great teacher. You inspire me.

Table of Contents

Biography ……2

Abstract ……3

Acknowledgements ……4

Table of Contents ……5

List of Tables ……6

List of Abbreviations……6

Background……7

Method ……9

Results ……10

Discussion……15

Conclusion……19

References ……21

Tables ……25

List of Tables

Table I: GRADE Evidence Profile

Table II: Key Characteristics

Table III: Summary of Findings

Table IV: Cross Validation Result

List of Abbreviations

DMD…….……...…Duchenne Muscular Dystrophy

EKG…….Electrocardiogram

Deflazacort Versus Prednisone: A Systematic Comparison of two Steroids in the Treatment of Duchenne Muscular Dystrophy

BACKGROUND

Duchenne muscular dystrophy (DMD) is an x-linked genetic pediatric disorder only affecting males involving the deletion or mutation of the Xp21 gene which produces the dystrophin protein. This crucial protein supports cell wall structure. Over time, a lack of functioning dystrophin leads to muscle cell weakness and degeneration with evident signs in patients as young as 6 years of age. It is theorized humoral and cellular immune responses in DMD contribute to the pathologic process of muscle cell wasting; further cell breakdown is produced by macrophages, cytotoxic t-cells, complement activation, and HLA class 1 antigens causing additional t-cell mediated attack. This damage to muscle cells has drastic implications on patients with muscle decline and can lead to loss of ambulation by 13 years of age,[5] progression of scoliosis once this has occured and cardiac and pulmonary function deterioration, resulting in reduced life expectancy.[6]

In 20% of DMD children, death is caused by cardiac complications.[6,7] Ninety percent of children with DMD have significant cardiac progression[8] with 20-30% showing evidence by the age of 10.[9,10] The test to first show detectable cardiac changes in DMD is the electrocardiogram (EKG) and these changes can be seen almost universally by 12 years of age.[11] Q-waves in lateral and inferolateral leads,[12-14] increased voltage in right precordial leads,[15] abnormalities in repolarisation, and an increased cardiomyopathic index[14] are four signs in the EKG showing cardiac damage. The Echocardiogram is the standard screening method for DMD cardiomyopathy which shows ventricular systolic dysfunction with a defect leading to chamber dilation.[13] Other cardiac complications in DMD patients include sinus tachycardia,[16] prolonged QT intervals,[17] and risk of emboli due to immobilization.[5] Cardiac biopsies in DMD children show hypertrophic

cardiomyocytes with increased internal nuclei, endocardial and interstitial fibrosis with cytoplasmic lipofuscinosis and focal lymphocytic infiltration, large pleomorphic bizarre nuclei, and vacuoles and focal necrosis.[18] Post-mortem cardiac tissue fiber analysis shows fibers are replaced by connective tissue and extensive myocardial fibrosis.[8,19]

Pulmonary dysfunction is the second deadly complication in DMD children. Pulmonary function decline begins with respiratory muscle weakness in the late teens. Nocturnal hypoventilation develops and eventually respiratory failure ensues. If patients continue untreated, death occurs in the late teens to twenties. However, treating with ventilation support can prolong life into the fourth decade.[5]

This raises the question how steroids affect DMD and prolong life suspending cardiac and pulmonary damage. Because DMD is a muscle wasting disease, treatment by steroids focuses on slowing the progression of muscle cell wall damage. Steroids have an anti-inflammatory, immunosuppressive affect.[20] Specifically, steroids inhibit muscle proteolysis,[21,22] stabilize muscle fiber membranes[23] and increase myogenic repair.[24] They reduce cytosolic calcium concentrations,[25-27] and differentiate regulation of genes in muscle fibers.[28] These actions, with suppression of the humoral and cellular immune responses, help to slow the progression of disease. In addition, steroids leave expression probes in whole blood which allow for deeper analysis of the functioning of each steroid.[29]

Today, the standard of care is to treat DMD patients with steroids. Deflazacort and prednisone, two steroids with similar chemical structures and relatively similar side effect profiles, are currently used in the treatment of DMD children. Deflazacort is not available in the US but is being used in Canada and Europe where most of the current literature on deflazacort is being produced. Deflazacort has demonstrated fewer adverse effects[30] and parents will order it from outside the US for treatment of their children at provider suggestion. Other families ultimately decline the use of any steroid to avoid side effects. Established dosing schedules have

still not been determined for either steroid with many studies presenting regimens to decide the best routine which both optimizes treatment outcomes while minimizing unwanted side effects. Most literature has been unable to state whether deflazacort is safer than, as efficacious as or carries the same risk of harm as prednisone. This systematic review attempts to compile studies that do adequately compare the two and report an overall consensus of conclusions. The goal is to highlight all outcomes to help support medical providers with decisions in regards to DMD treatment.

METHODS

Initial Search

A thorough and complete search of the literature was conducted for relevant research using the databases MEDLINE, CINAHL, Evidence Based Medicine Reviews Multifile and Web of Science. The key words used were muscular dystrophy, prednisone and deflazacort. An examination of titles and abstracts was conducted looking for relevant articles and collected as additional background sources. In the reference sections, all articles including the background sources and a similar systematic review were searched for further studies.

Eligibility Criteria

Studies must have been DMD pediatric male patients who were being treated with either prednisone or deflazacort and must have contained comparison statistics. Patient diagnostic criteria and evaluation for DMD had to be incorporated and assessed. Because of the progression of this disease and the limited amount of evidence reported, observational studies were included along with randomized control trials. Any and all study outcomes were considered to fully assess the comparison of the two steroids. The studies were excluded if they had other patient populations or did not specifically compare the two steroids one to the other.

Quality Assessment

The quality of literature was assessed using the GRADE system. GRADE evaluates studies based on design, execution, description, and explanation of data in the study.

RESULTS

Summary

The search strategy resulted in a total of 115 articles. After examination of titles and abstracts, four articles were selected for review.[1-4] Of the four studies included, one is a randomized control trial and three are retrospective cohort studies. Two studies[1,2] are of moderate quality and two studies[3,4] are very low quality. Because of the importance and relevance of this data to the DMD population and the limited studies available, very low quality studies were included knowing the conclusions presented are not definitive. Table 1 highlights the quality of each article and its importance. One study of moderate quality, Bonifati et al,[1] collected data outside the US in Italy. Table 2 focuses on the key characteristics of each study assessed. Table 3 focuses on the key outcomes from each study. Studies are reviewed in chronological order according to publication date.

Bonifati et al

Bonifati et al[1] is a randomized, double-blind study conducted over 12 months in Italy in 2000 with a sample size of 25 children. Patients were stratified by age and disease severity with both the patients and medical providers blinded to the use of either deflazacort or prednisone. There are 18 children treated with steroids, but the study does not state how many patients are in each specific steroid group. Inclusion criteria prevented patients from previous steroid use to enter the study. All patients were of similar ages and functional parameters; at baseline and throughout the study, biochemical and neurological screenings were conducted. Outcomes assessed include muscle strength and functional score, and significant side effects. There is one

loss to follow-up in the prednisone group due to loss of ambulation. The study corrects for differences in weight by suggesting a diet to the subjects.[1]

The results show there are no significant differences between steroids in terms of muscle strength and function. Both steroids significantly improve or delay muscle weakness. The study notes deflazacort has higher muscle assessment scores overall but it is not deemed a significant difference to prednisone. It suggests this may be due to the deflazacort group having better baseline values.[1]

There is, however, a significant difference in side effect profiles in this study. The prednisone group has a significant increase in weight gain compared to the deflazacort group. At six months, the first significant difference is seen as a percentage increase in weight from baseline. This trend continues on into the ninth month with 5% gain in the deflazacort group and 18% in the prednisone group and to a year with 9% gain in the deflazacort group and 21.3% gain in the prednisone group. The study also notes four patients taking prednisone had an increase in weight of over 20% of baseline but only one deflazacort patient did.[1]

In regards to other side effects, behavior changes, appetite increase, and the appearance of cushingoid features, all slightly increased but stayed equal between both groups. One child taking deflazacort reported a traumatic bone fracture whereas prednisone children had no fractures during the study. Cataracts were reported in both groups with two in deflazacort patients and one in a prednisone patient. All laboratory parameters remained either equal or unchanged in both groups.[2]

Balaban et al

The second study, Balaban et al,[2] published in 2005, is a retrospective cohort study of DMD boys conducted over seven years. The age range of 12-15 years is the age when patients finished the study. Data was collected from Colorado. Patients were not randomized; the family determined treatment after discussing with a medical provider the side effects and cost of each

medication. The article purposely emphasizes families choosing prednisone over deflazacort due to cost alone. Prognostic factors were relatively equal due to the nature of the DMD patient population. Balaban et al[2] assesses muscle strength and functionality, pulmonary efficiency, weight gain, cataracts, fractures, behavior changes and the presence of severe scoliosis with the recommendation for surgery.[2]

The main focus of the study was muscle functionality over time. There are two differences between prednisone and deflazacort groups. One is the deflazacort group's change in grip strength over the ages 10-15years which significantly increased ($p<0.05$). The second is the prednisone group had considerable improvement in pinch strength ($p<0.05$). All other values were relatively equal when comparing the steroids to each other. A note that is not statistically significant but important to mention is deflazacort patients had overall higher absolute muscle testing score values compared to prednisone. Additionally, this study compares each steroid to control values. Deflazacort boys were stronger compared to controls upon completion of the study, but prednisone boys were not. Overall, both groups preserved upper limb strength compared to controls.[2]

Weight gain was another major factor in this study. Deflazacort patients reported early weight gain at the beginning of the trial into the 25^{th} and 50^{th} percentiles at age 10. Prednisone patients at age 10 had weight gain into the 75^{th} and 90^{th} percentiles. By 12 years of age, deflazacort patients were holding steady in the 50^{th} to 75^{th} percentiles. Prednisone children at 12 years of age stayed in the 75^{th} and 90^{th} percentiles. Three prednisone treated boys had medication decreased or discontinued due to the unhealthy weight gain. No deflazacort patients had a change in medication dosage for weight.[2]

This trial considered pulmonary function. While it is clear that both steroids significantly improved compared to controls, no significant divergence is found between the two steroid groups. Even though it is not significantly different, the article does say deflazacort children

continued to have increasing forced vital capacity in the 10-15 year old age range whereas the prednisone children remained unchanged.[2]

Over the 7 year study period, scoliosis was continually assessed and managed as well. Deflazacort patients never met criteria for surgery. Two prednisone patients met conditions but only one had a scoliosis surgery while the family declined in the second case.[2]

Both groups had dosage tapers or discontinuations due to other side effects. The prednisone groups had one patient with a fracture and three patients with behavior changes. The fracture case and one of the behavior changing patients had dose tapering or discontinuation, not specifically specified by the article. The deflazacort group had one fracture, one behavior change patient and one patient with hypertension. All three of these subjects had tapering adjustments made.[2]

Markham et al

Markham et al[3] is a study collecting data in 2005, which strictly focuses on cardiac function in DMD patients and its relationship to steroids. Done in the US, it is a retrospective cohort which collected previous data on any DMD patient that had an echocardiogram assessing shortening fraction. Any patient under the age of 22 at the time of testing was included. This allowed for a statistically significant difference between the ages of the steroid groups with deflazacort patients being younger than the prednisone patients. The other prognostic factors including treatment length, weight, BMI, systolic and diastolic pressure and left ventricular end diastolic dimensions were equal.[3]

The results of Markham et al[3] show both groups to be equal. Whether a patient is on deflazacort or prednisone, the article's results show both steroids prevent cardiomyopathic progression. Both prednisone and deflazacort, even if discontinued after four years of treatment, still have cardiac protection for up to an additional six years.[3]

Lit et al

The last study published in 2008 takes a unique look at how steroids affect DMD patients. Lit et al[4] concentrates on whole blood gene expression. After collecting whole blood from 34 DMD patients, it is analyzed to determine how each steroid is expressed and if the samples can be differentiated one from the other. To test identification via genetic probes, the analyst was blinded. Two special case patients had taken prednisone first then switched to deflazacort by the time of testing so their specimens were used to assess results.[4]

Between steroid groups in expression, 508 probes were found to be statistically different. Deflazacort has probes with 478 lower expressions and 30 higher expressions than prednisone. Implementing these probes into a prediction analysis of microarrays system, 496 probes were found to completely separate deflazacort from prednisone. Further analysis of the two special case specimens with both steroids against the 508 probes revealed characteristics of prednisone expression. However, once tested with the 496 probes only one specimen was properly identified. Table 4 exhibits a ten-fold leave-one-out cross validation test displaying the accuracy of predicting the correct steroid based on the 496 probes.[4]

The most relevant data identified by this study is the type of probes each steroid is expressing. Deflazacort expresses a retinoic acid receptor α associated with inhibition of adipocyte differentiation. Prednisone, in opposition, expresses probes related to lipid metabolism, adipose formation and energy homeostasis. There are multiple probes which inhibit lipolysis in adipose tissue represented in the prednisone group, as well as interleukin systems one and six which both are linked with obesity.[4]

DISCUSSION

Muscle Function

As expected, the two studies assessing muscle functionality both generally concluded the same results.[1,2] Either steroid is sufficient in treating DMD children to prolong strength and ambulation. Despite the small differences in studies, both surprisingly state deflazacort has better absolute values compared to prednisone even though neither is statistically significant. With this statement it is perhaps necessary for further studies to evaluate and report if this could be significant either on a larger sample size or over a longer period of time. Because it is the gold standard to treat DMD patients with steroids it is perhaps more important to compare deflazacort and prednisone based on their side effects.

Weight Gain

Weight gain is the most substantially documented detrimental side effect from steroids to DMD boys in this review. Both Bonifati et al[1] and Balaban et al[2] show that prednisone significantly causes an increased gain in weight in the target population compared to deflazacort. Using Bonifati et al's[1] results for weight gain greater than 20% over baseline, the number needed to treat was three patients; meaning, treating three DMD children with deflazacort will get one better outcome in weight management than treating with prednisone. Because both groups have the same functional ability, it cannot be assumed the deflazacort group is more active compared to the prednisone group. This leads to the hypothesis that the drugs directly affect patient weight. Activity level, as a confounding variable, can be addressed in future studies by possibly assessing participants activity via questionnaire or even implementing a required activity class for a subgroup of each steroid.

Lit et al[4] gives the possible explanation for drastic differences in weight when defining gene expression probes for each steroid. Because prednisone expresses genetic probes in blood which are directly responsible for lipid metabolism and adipose formation,[31] it can be suggested

that prednisone is directly causing the weight gain seen in the other studies. Conversely, deflazacort has gene probes for retinoic acid that reduces obesity.[32,33] These two findings by Lit et al[4] can explain why, in Balaban et al,[2] deflazacort patients gained some initial weight but never became obese. Further research on whole blood genetic probes in this population may lead to more appropriate dosing regimens decreasing side effect incidence while maintaining therapeutic effect.

Cardiac Health

Cardiac function was only assessed in one study reviewed, Markham et al.[3] It clearly defines both steroids as sufficient in prolonging cardiac cell health. By sustaining cell health, DMD children will have a longer life expectancy which is critical. This study does suggest further evidence is needed by assessing cardiomyopathy with other tests. Since background studies show EKGs detecting the first signs of cardiomyopathies in DMD children, it would be helpful to see if there are differences in EKGs in each steroid group which could further differentiate deflazacort and prednisone.

Pulmonary Health

Balaban et al[2] is the only study to fully test lung function by measuring functional vital capacity regularly. In both drugs, functional capacity is preserved. Over time, it may be interesting to see if significant differences do develop since deflazacort did continue to increase vital capacity in the 10-15 year age range where prednisone continues to remain unchanged.

Scoliosis

Scoliosis was measured in Balaban et al[2] but not the other studies. With regards to DMD populations this may be a colossal omission in the current literature. Scoliosis progression in the adolescent years of life only hinders pulmonary and cardiac functions which are the leading contributors to death. Once independent ambulation is lost all other major functions to preserve life begin to deteriorate in DMD boys. Both prednisone and deflazacort significantly delay

scoliosis progression according to Balaban et al.[2] What was interesting but not deemed statistically significant during the seven year trial was that no deflazacort patients even met the criteria for scoliosis surgery where two prednisone patients did with one undergoing spine surgery. Further evaluation comparing deflazacort to prednisone with patients both ambulatory and non-ambulatory is warranted to define possible dissimilarities.

Gene Probes

In addition to the relevance of the specific gene probes identified linking weight gain in Lit et al,[4] it is important to note 496 probes have been identified which can accurately differentiate deflazacort from prednisone. This new research should continue to help in the treatment of DMD patients.

Minor Side Effects

Many minor side effects were determined to be the same or not significant between the two steroid groups. Only Bonifati et al[1] and Balaban et al[2] reviewed side effect profiles.

Cataracts - Both Bonifati et al[1] and Balaban et al[2] had patients with cataracts. Bonifati et al[1] had two deflazacort patients and one prednisone patient with cataracts and Balaban et al[2] had two and zero respectively. There was no statistical difference in either case.

Fractures – Bonifati et al[1] had one deflazacort patient with a fracture but no prednisone patients had fractures. Balaban et al[2] in each group had one fracture which resulted in a decrease is medication dose for both.

Behavior Changes – Balaban et al[2] had a total of four patients with behavior changes. In all cases, dosage adjustments were necessary with one treated with deflazacort and three treated with prednisone. Bonifati et al[1] reported changes in behavior in both groups but not to the point of changing prescriptions. It was disappointing neither study described the behavior changes. To decide if action is necessary, future studies should evaluate alterations in behavior and the correlation to each steroid in DMD males.

Cushingoid appearance – Bonifati et al[1] noted similar changes in both groups.

Appetite Increase – Bonifati et al[1] recorded comparable appetite increases. This helps further support previous statements about compared weight gain. Since both groups have similar appetites, it cannot be assumed the prednisone patients were eating more than deflazacort patients to allow for the considerable distinction. One issue not addressed is matching participants in age and the relation to appetite. In most cases, young children do not have comparable appetites to teenagers.

Hypertension – Hypertension was only assessed in the Balaban et al[2] article. Because of hypertension, one deflazacort patient had to decrease medication dosage. There was no record of hypertension in any prednisone patients.

Limitations of Study

Each study had its own limitations which is one reason this review was necessary. Pulling them together does not essentially make the evidence stronger but does show where holes in literature need to be addressed.

Bonifati et al[1] is the only randomized control trial but it was conducted over only one year. It had a small sample size and failed to define the number of patients in each group. Because just one patient was removed from the prednisone group in mid-study, the data was significantly altered. That one patient from the beginning of the study was declining rapidly in performance and had to drop out from loss of independent ambulation. It is possible with a larger sample size this would not have had such drastic implications.

Balaban et al[2] is perhaps the best conducted study despite being an observational retrospective cohort study. The only risk of bias is from families choosing medication prescribed based on known side effects and cost. It is regrettable most families made their decision on cost alone. In future studies, it would be optimal if the study researchers could eliminate the cost

factor by providing free or equally priced drugs to patients which was of course not possible in this retrospective study.

Markham et al,[3] another observational retrospective study, was limited due to inconsistency in age of the two groups studied. If the mean age groups were not different it's possible other conclusions could have been drawn. This damaged the study's quality; even if it had significant differences between steroids, its evidence could not be taken as fact.

The last study, Lit et al,[4] is of moderate quality as an observational study. No major limitations were identified. The significance of the gene probes discovered is critical to understanding how these steroids are really affecting the DMD patients. As much ongoing research in this area as possible can only improve the knowledge base.

CONCLUSION

Implications for Practice

The overall results of the combined studies are not able to reveal the absolute best steroid to treat DMD. If providers are specifically interested in avoiding weight gain, deflazacort should be prescribed over prednisone. All other patient important outcomes are relatively equal. Although it is not definitive, it seems once approved for use in the US, overall, deflazacort may hold some advantages over prednisone in treating DMD children.

Implications for Research

This review stresses the importance of more research comparing deflazacort and prednisone in randomized trials. This is a time sensitive issue; once the importance of deflazacort is truly realized, additional trials need to be conducted to make it available to the US population. Because it is unethical to not treat DMD patients with steroids, trials cannot have controls, unfortunately hindering the quality of evidence. However, since it is fully supported both steroids work to prolong muscle functionality, protect against cardiomyopathy and sustain pulmonary

health, randomizing patients into deflazacort and prednisone would be appropriate. Additionally, DMD patients are already regularly examined by a cardiologist, pulmonologist and additionally orthopedists for muscle function and scoliosis. If patients are willing to be randomized into either steroid group and difference in cost is eliminated, the next step would be to harvest the data collected by their regular primary providers. A study of this nature would be most beneficial to both providers and patients.

As technology and techniques improve more research in genetic testing in DMD patients will be valuable. There are many avenues to be explored and evaluated concerning genetic probes in whole blood and their implications in treating DMD children.

References

1. Bonifati MD, Ruzza G, Bonometto P, et al. A multicenter, double-blind, randomized trial of deflazacort versus prednisone in duchenne muscular dystrophy. *Muscle Nerve*. 2000;23:1344-1347.
2. Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in duchenne muscular dystrophy: Long-term effect. *Am J Phys Med Rehabil*. 2005;84:843-850.
3. Markham LW, Spicer RL, Khoury PR, Wong BL, Mathews KD, Cripe LH. Steroid therapy and cardiac function in duchenne muscular dystrophy. *Pediatr Cardiol*. 2005;26:768-771.
4. Lit L, Sharp FR, Apperson M, et al. Corticosteroid effects on blood gene expression in duchenne muscular dystrophy. *Pharmacogenomics Journal*. 2009;9:411-418.
5. Quinlivan R, Chikermane A, Bourke JP. Prevention and treatment for cardiac complications in Duchenne and Becker muscular dystrophy. *Cochrane Database of Systematic Reviews*. 2011;4.
6. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders*. 2002;12:926-929.
7. Muntoni F. Cardiomyopathy in muscular dystrophies. *Curr Opin Neurol*. 2003;16:577-583.
8. Heymsfield SB, McNish T, Perkins JV, Felner JM. Sequence of cardiac changes in Duchenne muscular dystrophy. *Am Heart J*. 1978;95:283-294.
9. Backman E, Nylander E. The heart in Duchenne muscular dystrophy: a non-invasive longitudinal study. *Eur Heart J*. 1992;13:1239-1244.
10. Finsterer J, Stollberger C. The heart in human dystrophinopathies. *Cardiology*. 2003;99:1-19.

11. Bies R, Friedman D, Roberts R, Perryman M, Caskey C. Expression and Localization of Dystrophin in Human Cardiac Purkinje-Fibers. *Circulation*. 1992;86:147-153.
12. Hoogerwaard EH, Voogt WG, Wilde A et al. Evolution of cardiac abnormalities in Back muscular dystrophy over a 13-year period. *Journal of Neurology*. 1997;244:657-663.
13. Nigro G, Comi LI, Politano L, Bain RJ. The incidence and evolution of cardiomyopathy in Duchenne muscular dystrophy. *Int J Cardiol*. 1990;26:271-277.
14. Nigro G, Comi LI, Politano L, et al. Evaluation of the cardiomyopathy in Becker muscular dystrophy. *Muscle Nerve*. 1995;18:283-291.
15. Nikolic G. Dominant R wave in lead V1. *Heart & Lung*. 1998;27:352-353.
16. Lanza GA, Dello Russo A, Giglio V, et al. Impairment of cardiac autonomic function in patients with Duchenne muscular dystrophy: relationship to myocardial and respiratory function. *Am Heart J*. 2001;141:808-812.
17. Nigro G, Comi LI, Limongelli FM, et al. Prospective study of X-linked progressive muscular dystrophy in Campania. *Muscle Nerve*. 1983;6:253-262.
18. Casazza F, Brambilla G, Salvato A, Morandi L, Gronda E, Bonacina E. Cardiac transplantation in Becker muscular dystrophy. *J Neurol*. 1988;235:496-498.
19. Oldfors A, Eriksson BO, Kyllerman M, Martinsson T, Wahlstrom J. Dilated cardiomyopathy and the dystrophin gene: an illustrated review. *Br Heart J*. 1994;72:344-348.
20. Kissel JT, Burrow K, Rammohan KW, Mendell JR. Monomuclear call analysis of muscle biopsies in prednisone-treated and untreated Duchenne muscular dystrophy. CIDD Study Group. *Neurology* 1991;41(5):667-72.
21. Elia M, Carter A, Bacon S, Winearls CG, Smith R. Clinical usefulness of urinary 3-methylhistidine excretion in indicating muscle protein breakdown. *British Medical Journal (Clinical Research Ed)* 1981;282(6261):351-4.

22. Rifai Z, Welle E, Moxley RT 3rd, Lorenson M, Griggs RC. Effect of prednisone on protein metabolism in Duchenne muscular dystrophy. *American Journal of Physiology* 1995;268(1pt1) E67-E74.
23. Jacobs SC, Bootsma AL, Willems PW, Bar PR, Wokke JH. Prednisone can protect against exercise-induced muscle damage. *J Neurol*. 1996;243:410-416.
24. Anderson JE, Weber M, Vargas C. Deflazacort increases laminin expression and myogenic repair, and induces early persistent functional gain in mdx mouse muscular dystrophy. *Cell Transplant*. 2000;9:551-564.
25. Metzinger L, Passaquin AC, Leijendekker WJ, Poindron P, Ruegg UT. Modulation by prednisolone of calcium handling in skeletal muscle cells. *Br J Pharmacol*. 1995;116:2811-2816.
26. Passaquin AC, Lhote P, Ruegg UT. Calcium influx inhibition by steroids and analogs in C2C12 skeletal muscle cells. *Br J Pharmacol*. 1998;124:1751-1759.
27. Vandebrouck C, Imbert N, Duport G, Cognard C, Raymond G. The effect of methylprednisolone on intracellular calcium of normal and dystrophic human skeletal muscle cells. *Neurosci Lett*. 1999;269:110-114.
28. Muntoni F, Fisher I, Morgan JE, Abraham D. Steroids in Duchenne muscular dystrophy: from clinical trials to genomic research. *Neuromuscular Disorders*. 2002;12:S162-5.
29. Wong B, Gilbert DL, Walker WL, et al. Gene expression in blood of subjects with Duchenne muscular dystrophy. *Neurogenetics*. 2009;10:117-125.
30. Bigger WD, Gingras M, Fehlings DL, Harris VA, Steele CA. Deflazacort treatment of Duchenne muscular dystrophy. *J Pediatr 2001*;138:45-50.
31. Strandberg L, Mellstrom D, Ljunggren O, et al. IL6 and IL1B Polymorphisms are Associated with fat mass in older men: The MrOS study Sweden. *Obesity*. 2008;16:710-713.

32. Redonnet A, Bonilla S, Noel-Suberville C, et al. Relationship between peroxisome proliferator-activated receptor gamma and retinoic acid receptor alpha gene expression in obese human adipose tissue. *International Journal of Obesity & Related Metabolic Disorders*. 2002;26:920.
33. Xue JC, Schwarz EJ, Chawla A, Lazar MA. Distinct stages in adipogenesis revealed by retinoid inhibition of differentiation after induction of PPARgamma. *Mol Cell Biol*. 1996;16:1567-1575.
34. Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. *Cochrane Database of Systematic Reviews*. 2008:003725.
35. Steare SE, Dubowitz V, Benatar A. Subclinical cardiomyopathy in Becker muscular dystrophy. *Br Heart J*. 1992;68:304-308.
36. Wong BL, Christopher C. Corticosteroids in Duchenne muscular dystrophy: a reappraisal. *J Child Neurol*. 2002;17:183-190.

Table I. GRADE Evidence Profile

Article	Design	Limitations	Inconsistency	Indirectness	Precision	Publication bias	Other Considerations	Magnitude of Effect	Dose-Response	Quality	Importance
Bonifati et al[1]	RCT	minus 1 pt drop changed analysis	0	0	minus 1 small sample	0	0	plus 1 wt change	0	moderate	important
Balaban et al[2]	retrospective cohort	0	0	0	0	0	0	0	plus 1	moderate	important
Markham et al[3]	retrospective cohort	0	minus 1 age difference	0	0	0	0	0	0	very low	critical
Lit et al[4]	retrospective cohort	0	0	0	0	0	0	plus 1	0	moderate	critical

Table II. Key Characteristics

Article	Design	# of Participants			Age Range	Length	Locations	Loss to Follow-up
		Deflazacort	Prednisone	Control				
Bonifati et al[1]	RCT	18		7	5.2-14.6	1yr	Italy	1 loss of ambulation
Balaban et al[2]	retrospective cohort	12	18	19	12.0-15	7yr	CO	
Markham et al[3]	retrospective cohort	19	29	63	<22	single test	OH, IO	
Lit et al[4]	retrospective cohort	6+-2	6+-2	20		single test	CA, OH	2 cross over

Table III. Summary of Findings

	Bonifati et al[1]		Balaban et al[2]		Markham et al[3]		Lit et al[4]	
Outcomes	Deflazacort	Prednisone	Deflazacort	Prednisone	Deflazacort	Prednisone	Deflazacort	Prednisone
Muscle Function	same	same	change in grip strength 10-15yrs	pinch strength change				
Weight	5% gain/9mo 9%/12mo	18% gain/9mo 21.3%/12mo	early gain	3 *				
Wt Gain > 20%	1	4						
Cataracts	2	1	2	0				
Fractures	1	0	1*	1*				
Behavior Change	same	same	1*	3*				
Cushingoid	same	same						
Appetite Increase	same	same						
Hypertension			1*	0				
Pulmonary			same	same				
Severe Scoliosis			0	2				
Cardiac Shortening Fraction					36.6%+-3.5	35%+-5.5		
Gene Expression							508 probes distinguish difference	
Specific Probes Identified							increased retinoic receptor alpha, fewer expression changes	increased probes for lipid metabolism and interleukin 1&6 associated with obestiy

* had to decrease or stop dose

Table IV. Cross-Validation Result

	Deflazacort	Prednisone
Number of Samples	6	6
Correct Prediction	6	6
Incorrect Prediction	0	0
Sensitivity	100%	100%
Specificity	100%	100%

Table IV. This cross-validation result shows that the 496 probes identified in Lit et al are both sensitive and specific in distinguishing between the two steroids, deflazacort and prednisone.